

Appln. No. 09/445,223
Amdt. dated October 7, 2003
Reply to Office action of May 7, 2003

REMARKS

Claims 5-8, 11, 22-24, 29, 30, 40-48 and 51-54 presently appear in this case. Claims 14, 15, 22, 29, 30, 40-43 and 49 have been withdrawn from consideration. No claims have been allowed. The official action of May 7, 2003 has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to DNA encoding a polypeptide which potentiates cell death and has the sequence of SEQ ID NO:1, as well as analogs and fragments thereof. The invention also relates to the polypeptides, vectors and host cells containing the DNA, and methods of producing the polypeptides using such a host cell, as well as the pharmaceutical compositions. The present invention is also directed to oligonucleotide molecules consisting of an antisense sequence of at least a part of an mRNA encoding a polypeptide of the present invention and a pharmaceutical composition containing such oligonucleotide. The invention further relates to a method of use of the DNA and polypeptides for modulating the effect of the B1 protein on the activity of inflammation or cell death or cell survival pathways or any other signaling activity.

After review and reconsideration, the examiner has agreed that example 17 should be applied to particular cases

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claiming a protein and a DNA encoding that protein. However, the examiner states that example 17 cannot be applied for the instant application, as the claims are not set forth in such a formula.

Claim 40 has now been amended so as to appear as an independent claim directed to protein X, wherein X is defined in paragraphs a, b and c. Claim 44 is directed to a DNA sequence encoding protein X, wherein protein X has the exact same definition as set forth in claim 40. Accordingly, the present claims use the same formula as is approved in example 17, and the examiner should now examine both the DNA and the protein claims.

The examiner states that the methods of use of the protein in claims 14, 15 and 49 are not rejoined because they are additional methods of use. Accordingly, claims 14, 15 and 49 have now been deleted without prejudice toward the continued prosecution thereof in a continuing application.

Accordingly, in light of this amendment of claim 40, it is requested that the restriction requirement be withdrawn and that all of the claims now present in the case be examined.

Claims 24 and 51-53 have been rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification. The examiner states that

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the specification does not teach an oligonucleotide molecule "consisting of" an anti-sense sequence.

The specification has now been amended at pages 13, 14 and 47 to correct an error with respect to the description of the anti-sense sequence. This is the same error that was noted by the examiner with respect to the corresponding claim language. As this was an obvious error, as was readily noted by the examiner, the correction of the specification does not involve new matter. Note that the term "anti-sense" was used in the specification as filed without this error at page 22, line 11, and page 32, line 10. Accordingly, claims 24 and 51-53 are now supported by the specification. Reconsideration and withdrawal of this rejection is respectfully urged.

Claims 5-8, 11, 23, 24, 44, 46, 51 and 52 have been rejected under 35 USC 112 first paragraph as failing to comply with the enablement requirement. The examiner states that these claims are drawn to a DNA sequence encoding a polypeptide comprising SEQ ID NO:1 or "an analog thereof having no more than 10 changes in the amino acid sequence each said change being a substitution, deletion or insertion of a single amino acid which analog potentiates cell death". The examiner states that the specification does not disclose the limitation of "an analog that has no more than 10 changes in the amino acid sequences of said DNA sequence each said change

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being a substitution, deletion or insertion of a single amino acid which analog potentiates cell death". This rejection is respectfully traversed.

First, it would appear that this rejection deals with the written description requirement and not the enablement requirement of the first paragraph of 35 USC 112. Second, the examiner's attention is invited to the present specification at page 24, lines 11-14, which states that one or more amino acids of this sequence may be replaced with another amino acid, deleted and/or inserted, provided that the resulting protein exhibits substantially the same or higher biological activity as the B1 protein to which it corresponds; page 14, line 17, which clarifies that there are preferably no more than 10 such changes; page 19, line 20, which states that a biological activity of B1 is enhancing cell death; and page 57, lines 30-31 which uses the terminology "potentiates the level of cell death". Accordingly, this language is fully and adequately supported by the specification. Reconsideration and withdrawal of this rejection is respectfully urged.

Claims 5-8, 11, 23, 24, 44-48 and 51-53 have been rejected under 35 USC 112, first paragraph, because the specification, while being enabling for an isolated cDNA sequence encoding a polypeptide comprising SEQ ID NO:1, does not reasonably provide enablement for a DNA sequence encoding

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a polypeptide comprising SEQ ID NO:1, an analog or fragment thereof. The examiner states that these claims encompass a genomic DNA sequence encoding a polypeptide comprising SEQ ID NO:1, an analog or fragment thereof. The examiner states that the specification discloses that the clone comprising the claimed polynucleotide sequence is isolated from cDNA libraries and one cannot extrapolate the teaching of the specification to the scope of the claims. This rejection is respectfully traversed.

The examiner's attention is drawn to the present specification at page 14, line 8, and page 16, line 21, where it states that the present invention can be carried out by screening either a cDNA library or a genomic DNA library. Thus, while the specific example used a cDNA library, those of ordinary skill in the art would understand that the same experiment could have been done by screening a genomic DNA library and that would have isolated the genomic DNA. Accordingly, the present specification does teach how to find the genomic DNA sequence and this can be identified without undue experimentation.

Furthermore, new claim 54 has now been added which specifies that the entire DNA is a coding region. This effectively excludes genomic DNA and includes not only cDNA but also synthetic DNA which encodes an analog or a fragment.

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Accordingly, at least new claim 54 should be considered to be free of this rejection.

Claims 5-8, 11, 23, 24, 44, 46, 51 and 52 have been rejected under 35 USC 112, first paragraph, because the specification, while being enabling for an isolated cDNA sequence encoding the polypeptide comprising SEQ ID NO:1, does not reasonably provide enablement for an analog of a DNA sequence encoding a polypeptide comprising SEQ ID NO:1, which analog potentiates cell death. The examiner states that protein chemistry is an unpredictable area of biotechnology, and in view of that unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed. This rejection is respectfully traversed.

The enablement requirement of 35 U.S.C. §112 is discussed at section 2164 *et seq* of the MPEP. MPEP §2164.01 states that any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contains sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The question is whether the experimentation needed to practice the invention is undue or unreasonable. If the invention can be practiced without undue

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or unreasonable experimentation, the enablement requirement is considered to be met. The undue experimentation factors of In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) are set forth at MPEP §2164.01(a). These factors include:

- (a) the breadth of the claims;
- (b) the nature of the invention;
- (c) the state of the prior art;
- (d) the level of one of ordinary skill;
- (e) the level of predictability in the art;
- (f) the amount of direction provided by the inventor;
- (g) the existence of working examples; and
- (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Here, the examiner takes the position that the scope of the claims is broader than the enabled disclosure, with respect to analogs thereof.

With respect to the breadth of the claims, part (b) of claim 44 specifies that the analogs have no more than ten changes in the amino acid sequence with each such change being a substitution, deletion or insertion of a single amino acid. It further specifies that the analog must potentiate cell death. It should be noted that the amino acid sequence of SEQ ID NO:1 has 540 residues. Thus, ten changes in the 540

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residue sequence amounts to less than 2%, i.e., the claimed analogs have a minimum of greater than 98% identity to the specified sequence.

The examiner's attention is invited to the Revised Interim Written Description Guidelines Training Materials, which have been published by the Patent and Trademark Office, Example 14 "Product by Function". There, a claim to a specific sequence and variants thereof that are at least 95% identical thereto and have a specified function was held to comply with the written description requirement. The Guidelines state:

The single species disclosed is representative of the genus because all members have at least 95% structural identity with the referenced compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

While these Training Materials relate to written description, rather than enablement, they should be instructive also from the standpoint of enablement to the extent that the Patent and Trademark Office has conceded that, with a claim such as the present, a single example is representative of the entire genus of variants with 95%

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identity. Thus, this is not a particularly wide breadth for an analog claim.

While claim 44 is somewhat broader than the DNA encoding the B1 protein of SEQ ID NO:1, the claimed scope is necessary in order to reasonably cover the invention. In MPEP §2164.08. relating to enablement commensurate in scope with the claims, the MPEP quotes the following from *In re Goffe*, 191 USPQ 429, 431 (CCPA 1976):

[T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

It should be noted that the definition of analog at claim 44(b) requires that the analog have the ability to potentiate cell death. In view of the stated activity and the direction in the specification, which will be discussed below, and the reasonable breadth of the analogs, the breadth is not unduly broad and the experimentation to find everything within the scope of these claims would not be undue.

The nature of the invention is such that substantial experimentation is reasonably conducted by those of ordinary skill in the art. The present claims are directed to recombinantly-produced polypeptides and DNA encoding same.

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Applicants concede that there is not 100% predictability in these fields. However, this does not mean that an applicant must be limited to exemplified embodiments. As long as it is shown that the experimentation to determine what falls within the claim is not undue, the enablement requirement is met. As discussed below, the experimentation is not undue.

As to the state of the prior art, there is no close prior art.

As to the level of one of ordinary skill, inventions involving biotechnology involve a very high level of ordinary skill. Because of this extremely high level of ordinary skill, even complex experimentation is not necessarily undue or unreasonable.

The next two *Wands* factors, the level of the predictability in the art and the amount of direction provided by the inventor, go hand in hand. As to the predictability in the art, when changing the sequence by less than 2%, there would be an expectation that the function is maintained. Thus, it is reasonably predictable that such a small number of changes will not destroy the activity, but in any event, it is readily testable in order to determine which will have the claimed function and which will not have the claimed function. The present claim always requires that the result of the amino

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acid changes have the ability to bind to potentiate cell death, i.e., by definition, the activity must be retained.

The present specification states at page 24, lines 18-25:

While any technique can be used to find potentially biologically active proteins which substantially correspond to B1 proteins, one such technique is the use of conventional mutagenesis techniques on the DNA encoding the protein, resulting in a few modifications. The proteins expressed by such clones can then be screened for their ability to bind to various other proteins having, for example, prodomains (CARD), kinase binding sites, or to B1 itself, and to modulate the activity of these other proteins or B1 itself in the modulation/mediation of the intracellular pathways noted above.

See also page 27, lines 16-19, where it states:

When the exact effect of the substitution or deletion is to be confirmed, one skilled in the art will appreciate that the effect of the substitution(s), deletion(s), etc., will be evaluated by routine binding and cell death assays. Screening using such a standard test does not involve undue experimentation.

Furthermore, substantial guidance is provided in the present specification as to preferred substitutions which would be expected to retain the activity of the base compounds, i.e., the B1 protein. Note, for example, page 24, line 26, through page 27, line 19.

The examples in the present specification, such as Example 2 (ii) (pages 55-56) and Example 3 in the first

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paragraph of page 57, show well-known cell death assays. These are relatively simple tests. They can be adapted to high throughput processes. This is not undue experimentation in this art, particularly in view of the small number of amino acids that may be changed in accordance with the language of the claims. Accordingly, it is apparent that there is substantial direction provided in the specification about how to do these standard assays. This is all that is necessary to do in order to determine whether any given analog having no more than ten amino acid changes has the ability to potentiate cell death. These minor changes are not unreasonable. Accordingly, substantial direction is provided by the specification.

As far as working examples are concerned, as discussed above, working examples of cell death assays are given in the specification and the effect of B1 proteins in these assays is provided in working examples. Mutants of B1 are also tested in working example 3. Furthermore, the guidance of the specification explains how to determine whether any given compound falls within the scope of the claims, and therefore additional working examples are not necessary.

Finally, the last *Wands* factor is the quantity of experimentation needed to make or use the invention based on

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the content of the disclosure. It is true that substantial experimentation will be necessary. However, as stated at MPEP §2164.06, the test is not merely quantitative since a considerable amount of experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Time and expense are not the controlling factors. Procedures for making variants of the B1 protein which have at least 98% identity with the sequence thereof are conventional in the art. See page 33, lines 18-21, where the present specification states:

While any technique can be used to find potentially biologically active proteins which substantially correspond to B1 proteins, one such technique is the use of conventional mutagenesis techniques on the DNA encoding the protein, resulting in a few modifications.

The assays involved to determine whether any such analog has the ability to potentiate cell death are routine, as is disclosed in the specification and discussed above. All of the claimed analogs must possess the specified activity of being able to potentiate cell death. There is a reduction to practice of the disclosed species of B1 protein. The fact that any single amino acid change might have a profound effect or no effect, is not really dispositive. Here, standard assays are provided in the specification and so any given

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analog can readily be tested without undue experimentation. Thus, applicants need not rely upon predictability of analogs with respect to changes (even though there is reasonable predictability with analogs of greater than 98% identity), but is relying on testing in the standard assays described in the specification which can be carried out in large numbers at the same time.

The level of skill in the art is high and the assays are standard and can be conducted with many different analog sequences at the same time. Thus, while substantial experimentation may be needed to establish all of the sequences of which fall within the scope of the claim, i.e., meet the functional requirement of potentiating cell death, such experimentation is not undue or unreasonable. Indeed, for any given sequence, the testing is virtually negligible in order to test for potentiating cell death.

For all of these reasons, the enablement requirement is fulfilled with respect to the full scope of claim 44. If there is enablement for the DNA of claim 44, there must be enablement for the polypeptides of claim 40 encoded by same and the other claims which depend therefrom. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

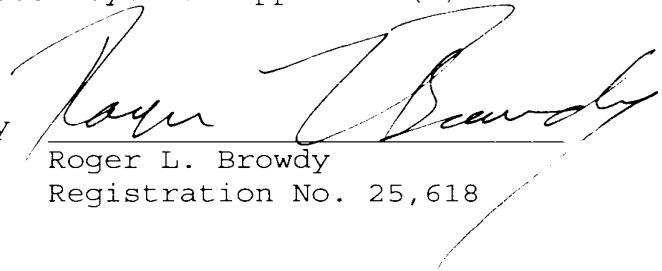
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It is submitted that all of the claims now present
in the case clearly define over the references of record, and
fully comply with 35 USC 112. Reconsideration and allowance
are therefore earnestly solicited.

Respectfully submitted,

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